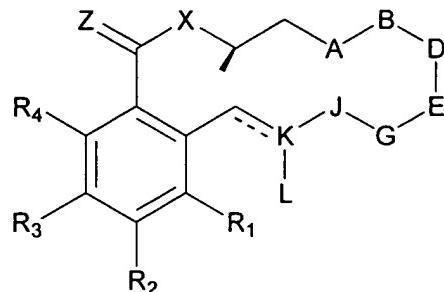


1
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3

CLAIMS

4 1. A compound having the structure:

5



6
7 wherein the dotted line --- represents a bond, whereby a double bond is present, or the
8 dotted line --- is absent, whereby a single bond is present;

9
10 R₁ is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
11 alkylheteroaryl moiety, or N(R_A)₂, wherein each occurrence of R_A is independently hydrogen, a
12 protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
13 moiety;

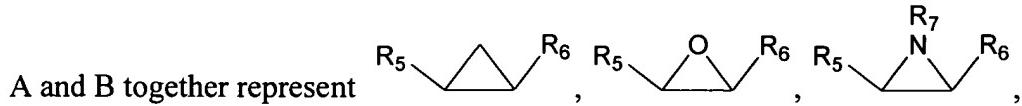
14 R₂ is hydrogen, halogen, cyano, -OR_B, -N(R_B)₂, -SR_B, -O(C=O)R_B, -N(R_B)(C=O)(R_B),
15 -C(O)R_B, -C(O)OR_B, -CON(R_B)₂, -OCO₂R_B, or an aliphatic, heteroaliphatic, aryl, heteroaryl,
16 alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_B is independently hydrogen, a
17 protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
moiety;

18 R₃ is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
19 alkylheteroaryl moiety, or -N(R_C)₂, wherein each occurrence of R_C is independently hydrogen, a
20 protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
21 moiety;

22 R₄ is hydrogen, halogen, cyano, -OR_D, -N(R_D)₂, -SR_D, -O(C=O)R_D, -N(R_D)(C=O)(R_D),
23 -C(O)R_D, -C(O)OR_D, -CON(R_D)₂, -OCO₂R_D, or an aliphatic, heteroaliphatic, aryl, heteroaryl,
24 alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_D is independently hydrogen, a
25 protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
26 moiety;

1 Z is O, S or NR_E, wherein R_E is hydrogen, a protecting group, an aliphatic,
2 heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or OR_F, wherein R_F is
3 hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
4 alkylheteroaryl moiety;

5 X is O, S or NR_G, wherein R_G is hydrogen or lower alkyl;



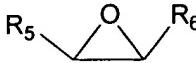
7 -CHR₅-CHR₆-, -CR₅=CR₆-, wherein R₅ and R₆ are each independently hydrogen, halogen,
8 cyano, -OR_J, -N(R_J)₂, -SR_J, -O(C=O)R_J, -O(S=O)R_J, -N(R_J)(C=O)(R_J), -C(=O)R_J, -C(=O)OR_J,
9 -CON(R_J)₂, -OCO₂R_J, -OS(=O)OR_J or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
10 alkylheteroaryl moiety, wherein each occurrence of R_J is independently hydrogen, a protecting
H group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and
12 wherein R₇ is hydrogen, a protecting group, -OR_K, -SR_K, -C(O)OR_K, -C(O)NR_K, -S(O)₂R_K, -
13 O(C=O)R_K, -N(R_K)(C=O)(R_K), -C(O)R_K, -C(O)OR_K, -CON(R_K)₂, -OCO₂R_K, or an aliphatic,
14 heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence
15 of R_K is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl,
16 heteroaryl, alkylaryl, or alkylheteroaryl moiety, or when A and B together represent -CHR₅-
17 CHR₆-, R₅ and R₆ taken together represent a substituted or unsubstituted 3-7 membered aliphatic,
18 heteroaliphatic, aryl or heteroaryl ring,

19 D and E together represent -CHR₈-CHR₉-, -CR₈=CR₉-, wherein R₈ and R₉ are each
20 independently hydrogen or lower alkyl;

21 G and J together represent -CHR₁₀-CHR₁₁-, -CR₁₀=CR₁₁-, wherein R₁₀ and R₁₁ are each
22 independently hydrogen or lower alkyl;

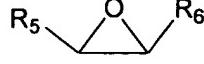
23 K and L together represent C=O, C=S, CH-CH₃, CH-CH(R_L)₂, C=C(R_L)₂, -CH₂-,
24 -C(-S(CH₂)₃S)-, CH-OR_L, CH-SR_L, CH-N(R_L)₂, CH-N(R_L)(C=O)(R_L), C=N-O-R_L, CH-N=O,
25 C=C(R_L)-N(R_L)₂, C=N-R_L, C=N-N(R_L)₂, or, if the dotted line --- represents a bond, whereby a
26 double bond is present, then K and L together represent C-N(R_L)₂, wherein each occurrence of
27 R_L is independently hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl,
28 alkylaryl, or alkylheteroaryl moiety, or two occurrences of R_L taken together represent a 3 to 7-
29 membered cyclic aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety;

1 whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently
2 be substituted or unsubstituted, cyclic or acyclic, or branched or unbranched, and each aryl,
3 heteroaryl, alkylaryl, and alkylheteroaryl moiety may be substituted or unsubstituted;
4 wherein one or any two of R₁, R_A, R₂, R_B, R₃, R_C, R₄, R_D, R₅, R₆, R_J, or R_L are optionally
5 a linker covalently bonded to a compound selected from the group consisting of radicicol,
6 monocillin, analogues of radicicol and monocillin, geldanamycin, analogues of geldanamycin,
7 and steroids; and
8 pharmaceutically acceptable derivatives thereof,
9 with the proviso that:

10 (1) if Z is O; if X is O; if A and B together are  and R₅ and R₆ are each
11 hydrogen; if D and E together are -CH=CH-; if G and J together are -CH=CH- ; if K and L
12 together are C=O; if R₁ is hydrogen or Cl; and if R₃ is hydrogen,

13 then R₂ is not -OR_B or -O(C=O)R_B, wherein R_B is hydrogen or an alkyl, alkoxy, alkenyl,
14 alkenyloxy, alkynyl, aryl, aryloxy, heterocycle, cycloalkyl, cycloalkenyl, or cycloalkenyl fused
15 to an aryl group; and R₄ is not -OR_D or -O(C=O)R_D, wherein R_D is hydrogen or an alkyl, alkoxy,
16 alkenyl, alkenyloxy, alkynyl, aryl, aryloxy, heterocycle, cycloalkyl, cycloalkenyl, or
17 cycloalkenyl fused to an aryl group;

18
19 (2) if Z is O; if X is O, if R₁ is Cl; if R₂ is OR_A and R_A is hydrogen, alkanoyl, alkenoyl,
20 tert-butyl dimethylsilyl or tert-butyldiphenylsilyl; if R₃ is hydrogen; if R₄ is OR_B and R_B is
21 hydrogen, alkanoyl, alkenoyl, tert-butyldimethylsilyl, or tert-butyldiphenylsilyl; if D and E
22 together are -CH=CH-; if G and J together are -CH=CH-; if A and B together are

23  or if A and B together are -CHR₅-CHR₆- and R₆ is halogen and R₅ is OR_J,
24 wherein R_J is hydrogen, alkanoyl, or alkenoyl, or R₅ is -O(S=O) R_J, wherein R_J is a second
25 compound of formula (I) linked via an oxygen atom present at R₅ in the second compound, and
26 wherein R₆ is halogen; Z is O; X is O, R₁ is Cl; R₂ is OR_A and R_A is hydrogen, alkanoyl,
27 alkenoyl, tert-butyl dimethylsilyl or tert-butyldiphenylsilyl; R₃ is hydrogen; R₄ is OR_B and R_B is
28 hydrogen, alkanoyl, alkenoyl, tert-butyldimethylsilyl, or tert-butyldiphenylsilyl;

1 then K and L together are not C=O or C=N-O-R_L, when R_L is hydrogen, or substituted or
2 unsubstituted lower alkyl, a substituted or unsubstituted alkylene moiety, a substituted carbonyl
3 moiety or a substituted or unsubstituted aryl moiety;

4 except that K and L together can be C=N-O-R_L, when R_L is a linker covalently bonded to
5 a compound selected from the group consisting of radicicol, monocillin, analogues of radicicol
6 and monocillin, geldanamycin, analogues of geldanamycin, and steroids; or

7

8 2. The method of claim 1, wherein one or any two of R₁, R_A, R₂, R_B, R₃, R_C, R₄, R_D, R₅, R₆,
9 R_J, or R_L are a linker covalently bonded to a compound selected from the group consisting of
10 radicicol, monocillin, analogues of radicicol and monocillin, geldanamycin, analogues of
11 geldanamycin, and steroids, wherein the linker is an aliphatic or heteroaliphatic moiety, whereby
12 said aliphatic or heteroaliphatic moiety is substituted or unsubstituted, branched or unbranched,
13 or cyclic or acyclic.

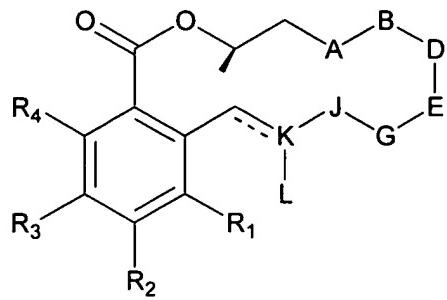
14

15 3. The method of claim 1, wherein one or any two of R₁, R_A, R₂, R_B, R₃, R_C, R₄, R_D, R₅, R₆,
16 R_J, or R_L are a linker covalently bonded to a compound selected from the group consisting of
17 radicicol, monocillin, analogues of radicicol and monocillin, geldanamycin, analogues of
18 geldanamycin, and steroids, wherein the linker is a moiety having one of the structures -(CH₂)_n-
19 CH=CH-(CH₂)_m-, -(CH₂)_p-C≡C-(CH₂)_q-, or -CH₂(CH₂)_sCH₂-, wherein each occurrence of n, m,
20 p, q and s is independently an integer from 0-10, and wherein one or more of the hydrogen atoms
21 are optionally replaced with an alkyl, heteroalkyl, aryl, heteroaryl, alkylaryl or alkylheteroaryl
22 moiety or a secondary or tertiary amine, hydroxyl, or thiol.

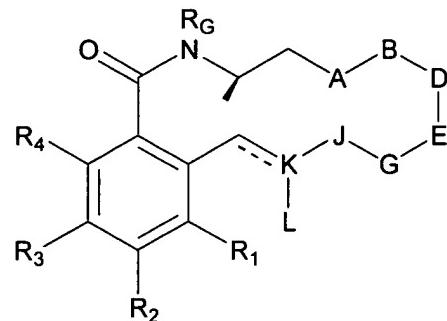
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24 4. The compound of claim 1, wherein Z and X are each O, and the compound has the
25 structure:

26

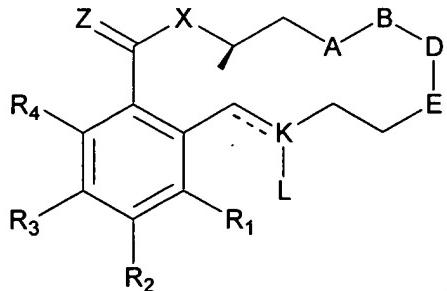


- 3 5. The compound of claim 1, wherein Z is O and X is NR_G, and the compound has the
4 structure:

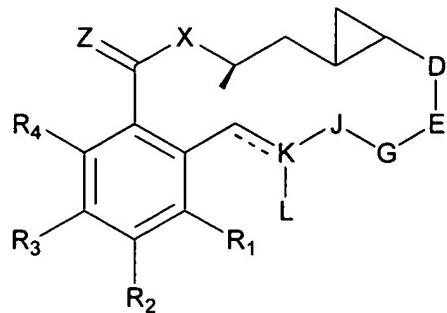


- 8 6. The compound of claim 5, wherein R_G is H.

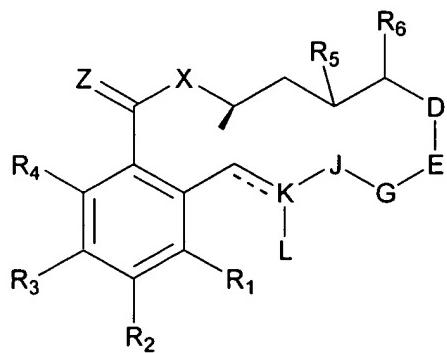
- 9 7. The compound of claim 1, wherein G and J together represent -CH₂-CH₂- and the
10 compound has the structure:



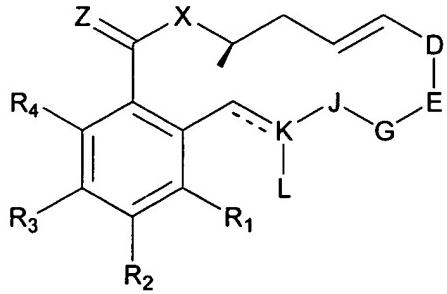
- 11
- 12
- 13 8. The compound of claim 1, wherein A-B is a cyclopropyl ring and the compound has the
14 structure:



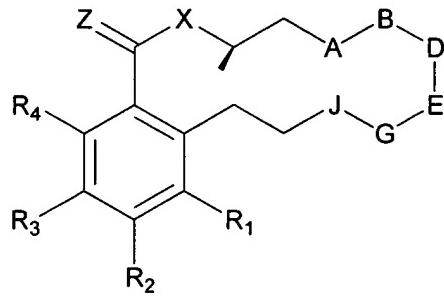
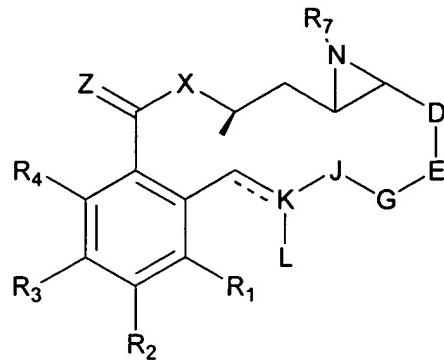
9. The compound of claim 1, wherein A and B together represent -CHR₅-CHR₆- and the compound has the structure:



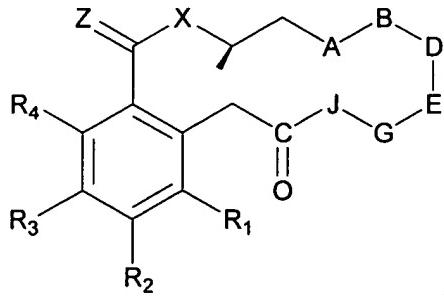
10. The compound of claim 1, wherein A and B together represent -CH=CH- and the compound has the structure:



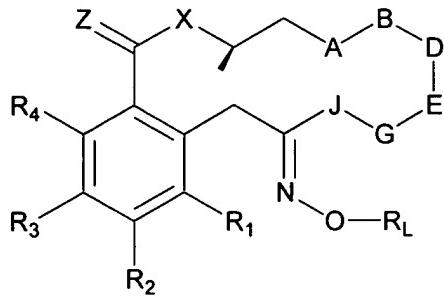
11. The compound of claim 1, wherein A and B together represent an aziridine and the compound has the structure:



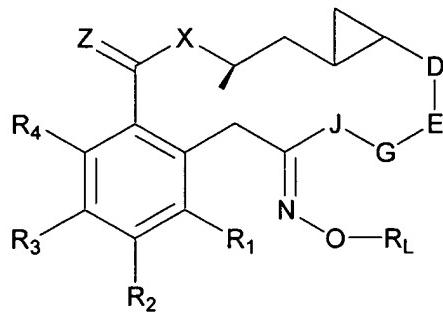
12. The compound of claim 1, wherein the dotted line --- is absent whereby a single bond is present, K and L together represent -CH₂- and the compound has the structure:



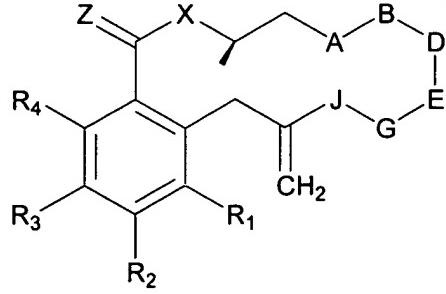
13. The compound of claim 1, wherein the dotted line --- is absent whereby a single bond is present, K-L together represent C=O and the compound has the structure:



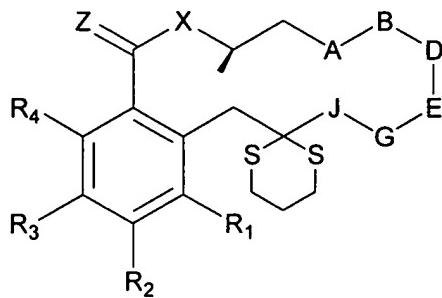
3 15. The compound of claim 1, wherein the dotted line --- is absent whereby a single bond is
4 present, A and B together represent a cyclopropyl group, K and L together represent C=N-O-R_L
5 and the compound has the structure:



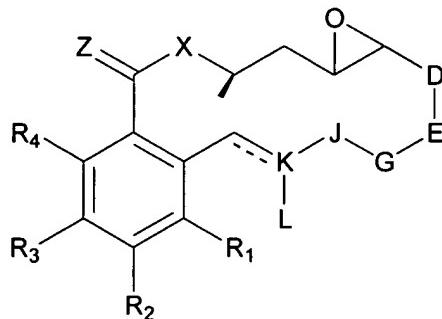
8 16. The compound of claim 1, wherein the dotted line --- is absent whereby a single bond is
9 present, K and L together represent C=CH₂ and the compound has the structure:



12 17. The compound of claim 1, wherein the dotted line --- is absent whereby a single bond is
13 present, K and L together represent a dithiane, -C(-S(CH₂)₃S-)-, and the compound has the
14 structure:



18. The compound of claim 1, wherein A and B together represent an epoxide and the compound has the structure:



wherein if Z is O and X is O, then at least one of the D-E, G-J, K-L, R₂ and R₄ are defined as:

R₂ is hydrogen, halogen, cyano, -N(R_B)₂, -SR_B, -N(R_B)(C=O)(R_B); -C(O)R_B, -C(O)OR_B, -CON(R_B)₂, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_B is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R₃ is not hydrogen;

R₄ is hydrogen, halogen, cyano, -N(R_D)₂, -SR_D, -N(R_D)(C=O)(R_D), -C(O)R_D, -C(O)OR_D, -CON(R_D)₂, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_D is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

D and E together represent -CHR₈-CHR₉- wherein R₈ and R₉ are each independently hydrogen or lower alkyl;

G and J together represent -CHR₁₀-CHR₁₁-, wherein R₁₀ and R₁₁ are each independently hydrogen or lower alkyl;

1 K and L together represent C=S, CH-CH₃, CH-CH(R_L)₂, C=C(R_L)₂, -CH₂-,
2 -C(-S(CH₂)₃S)-, CH-OR_L, CH-SR_L, CH-N(R_L)₂, CH-N(R_L)(C=O)(R_L), CH-N=O, C=C(R_L)-
3 N(R_L)₂, C=N-R_L, C=N-N(R_L)₂, or, if the dotted line --- represents a bond, whereby a double
4 bond is present, then K and L together represent C-N(R_L)₂, wherein each occurrence of R_L is
5 independently hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl,
6 alkylaryl, or alkylheteroaryl moiety, or two occurrences of R_L taken together represent a 3 to 7-
7 membered cyclic aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety; or
8 any two of R_I, R_A, R₂, R_B, R₃, R_C, R₄, R_D, R₅, R₆, R_J, or R_L are a linker covalently bonded to a
9 compound selected from the group consisting of radicicol, monocillin, analogues of radicicol and
10 monocillin, geldanamycin, analogues of geldanamycin, and steroids.

11

12 19. The compound of claim 1, wherein A and B together are -CHR₅-CHR₆- or -CR₅=CR₆-
13 and R₅ and R₆ are each independently hydrogen, halogen, cyano, -OR_J, -N(R_J)₂, -SR_J, -
14 O(C=O)R_J, O(S=O)R_J, -N(R_J)(C=O)(R_J), -OCO₂R_J or -OSO₂R_J and each occurrence of R_J is
15 independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl,
16 alkylaryl, or alkylheteroaryl moiety.

17

18 20. The compound of claim 19, wherein R₅ and R₆ are each independently hydrogen, or
19 lower alkyl.

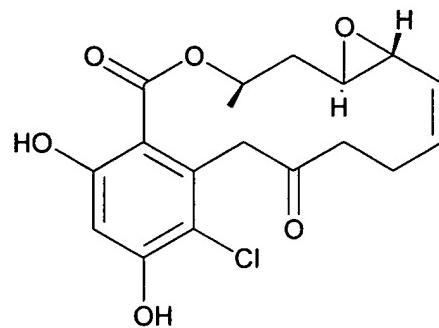
20

21 21. The compound of claim 1, wherein R₁ and R₃ are each independently halogen, hydrogen,
22 or lower alkyl; R₂ is hydrogen or -OR_B, wherein each occurrence of R_B is independently
23 hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
24 alkylheteroaryl moiety, and R₄ is hydrogen or -OR_D, wherein each occurrence of R_D is
25 independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl,
26 alkylaryl, or alkylheteroaryl moiety.

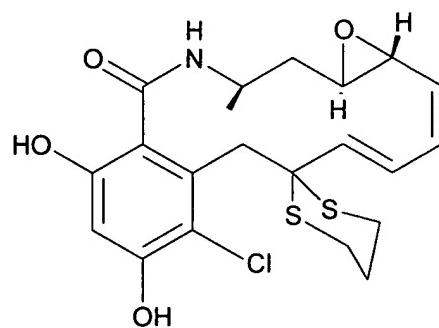
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28 22. The compound of claim 1, wherein the compound has the structure:

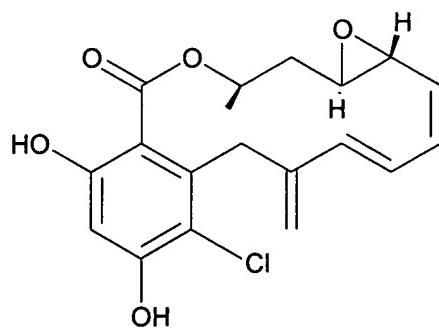
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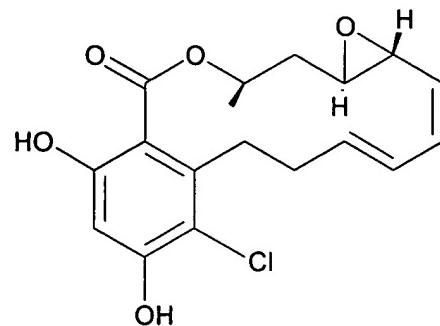
23. The compound of claim 1, wherein the compound has the structure:



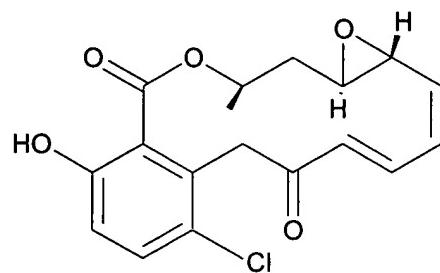
24. The compound of claim 1, wherein the compound has the structure:



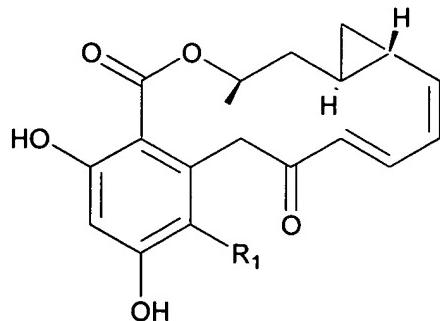
25. The compound of claim 1, wherein the compound has the structure:



26. The compound of claim 1, wherein the compound has the structure:



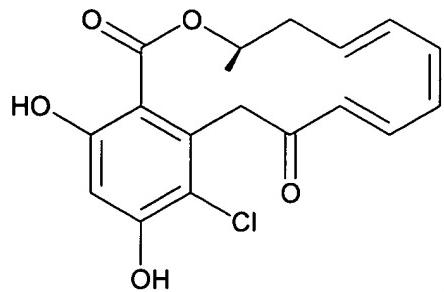
27. The compound of claim 1, wherein the compound has the structure:



wherein R₁ is hydrogen or Cl.

28. The compound of claim 1, wherein the compound has the structure:

14

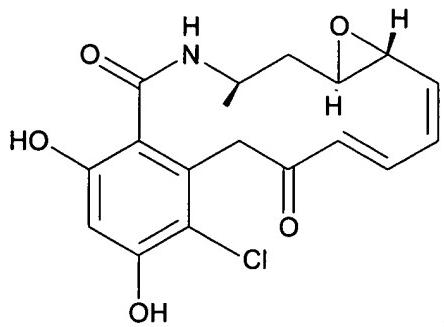


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3 29. The compound of claim 1, wherein the compound has the structure:

4



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30. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

12

13 32. The pharmaceutical composition of claim 31, wherein the one or more additional
14 therapeutic agents comprises an anticancer agent.

15

16 33. A method for treating cancer comprising:

17 administering a therapeutically effective amount of a compound of claim 1 to a subject in
18 need thereof.

19

20 34. The method of claim 33, wherein the therapeutically effective amount is in the range of
21 0.001 mg/kg to 50 mg/kg of body weight.

1
2 35. The method of claim 33, wherein the therapeutically effective amount is in the range of
3 0.01 mg/kg to about 25 mg/kg of body weight.

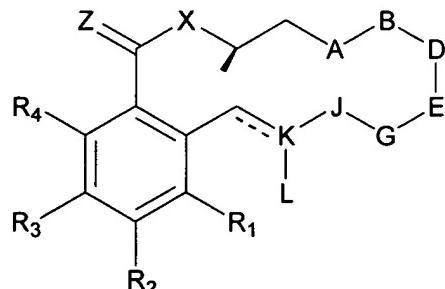
4
5 36. The method of claim 33, said method further comprising administering one or more
6 additional therapeutic agents in combination with the compound.

7
8 37. The method of claim 36, wherein the one or more additional therapeutic agents comprises
9 an anticancer agent.

10
11 38. A method for inhibiting the growth of or killing cancer cells, said method comprising:
12 contacting the cancer cells with an amount of a compound of claim 1 effective to inhibit
13 the growth of or kill cancer cells.

14
15 39. A method for treating a cancer in which the cancer cells comprise Rb negative cancer
16 cells, said method comprising:

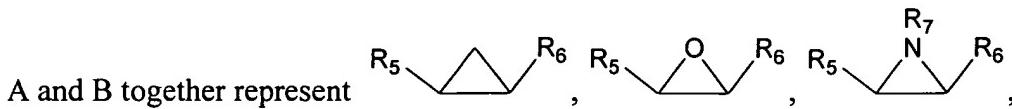
17 administering a therapeutically effective amount of a compound to a subject in need
18 thereof, which therapeutically effective amount is sufficient to inhibit the growth of or kill Rb
19 negative cancer cells, which compound has the structure:



22 wherein the dotted line --- represents a bond, whereby a double bond is present, or the
23 dotted line --- is absent, whereby a single bond is present;

24 R_1 is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
25 alkylheteroaryl moiety, or $N(R_A)_2$, wherein each occurrence of R_A is independently hydrogen, a

1 protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
 2 moiety;
 3 R₂ is hydrogen, halogen, cyano, -OR_B, -N(R_B)₂, -SR_B, -O(C=O)R_B, -N(R_B)(C=O)(R_B),
 4 -C(O)R_B, -C(O)OR_B, -CON(R_B)₂, -OCO₂R_B, or an aliphatic, heteroaliphatic, aryl, heteroaryl,
 5 alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_B is independently hydrogen, a
 6 protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
 7 moiety;
 8 R₃ is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
 9 alkylheteroaryl moiety, or -N(R_C)₂, wherein each occurrence of R_C is independently hydrogen, a
 10 protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
 11 moiety;
 12 R₄ is hydrogen, halogen, cyano, -OR_D, -N(R_D)₂, -SR_D, -O(C=O)R_D, -N(R_D)(C=O)(R_D),
 13 -C(O)R_D, -C(O)OR_D, -CON(R_D)₂, -OCO₂R_D, or an aliphatic, heteroaliphatic, aryl, heteroaryl,
 14 alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_D is independently hydrogen, a
 15 protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
 16 moiety;
 17 Z is O, S or NR_E, wherein R_E is hydrogen, a protecting group, an aliphatic,
 18 heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or OR_F, wherein R_F is
 19 hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
 20 alkylheteroaryl moiety;
 21 X is O, S or NR_G, wherein R_G is hydrogen or lower alkyl;



23 -CHR₅-CHR₆- , -CR₅=CR₆- , wherein R₅ and R₆ are each independently hydrogen, halogen,
 24 cyano, -OR_J, -N(R_J)₂, -SR_J, -O(C=O)R_J, -O(S=O)R_J , -N(R_J)(C=O)(R_J), -C(=O)R_J, -C(=O)OR_J,
 25 -CON(R_J)₂, -OCO₂R_J, -OS(=O)OR_J or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
 26 alkylheteroaryl moiety, wherein each occurrence of R_J is independently hydrogen, a protecting
 27 group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and
 28 wherein R₇ is hydrogen, a protecting group, -OR_K, -SR_K, -C(O)OR_K, -C(O)NR_K, -S(O)₂R_K , -
 29 O(C=O)R_K, -N(R_K)(C=O)(R_K), -C(O)R_K, -C(O)OR_K, -CON(R_K)₂, -OCO₂R_K, or an aliphatic,
 30 heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence

1 of R_K is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl,
2 heteroaryl, alkylaryl, or alkylheteroaryl moiety, or when A and B together represent -CHR₅-
3 CHR₆-, R₅ and R₆ taken together represent a substituted or unsubstituted 3-7 membered aliphatic,
4 heteroaliphatic, aryl or heteroaryl ring,

5 D and E together represent -CHR₈-CHR₉-, -CR₈=CR₉-, wherein R₈ and R₉ are each
6 independently hydrogen or lower alkyl;

7 G and J together represent -CHR₁₀-CHR₁₁-, -CR₁₀=CR₁₁-, wherein R₁₀ and R₁₁ are each
8 independently hydrogen or lower alkyl;

9 K and L together represent C=O, C=S, CH-CH₃, CH-CH(R_L)₂, C=C(R_L)₂, -CH₂-,
10 -C(-S(CH₂)₃S)-, CH-OR_L, CH-SR_L, CH-N(R_L)₂, CH-N(R_L)(C=O)(R_L), C=N-O-R_L, CH-N=O,
11 C=C(R_L)-N(R_L)₂, C=N-R_L, C=N-N(R_L)₂, or, if the dotted line --- represents a bond, whereby a
12 double bond is present, then K and L together represent C-N(R_L)₂, wherein each occurrence of
13 R_L is independently hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl,
14 alkylaryl, or alkylheteroaryl moiety, or two occurrences of R_L taken together represent a 3 to 7-
15 membered cyclic aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety;

16 whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently
17 be substituted or unsubstituted, cyclic or acyclic, or branched or unbranched, and each aryl,
18 heteroaryl, alkylaryl, and alkylheteroaryl moiety may be substituted or unsubstituted;

19 wherein one or any two of R₁, R_A, R₂, R_B, R₃, R_C, R₄, R_D, R₅, R₆, R_J, or R_L are optionally
20 a linker covalently bonded to a compound selected from the group consisting of radicicol,
21 monocillin, analogues of radicicol and monocillin, geldanamycin, analogues of geldanamycin,
22 and steroids; and

23 pharmaceutically acceptable derivatives thereof.

24

25 40. The method of claim 39, wherein the therapeutically effective amount is in the range of
26 0.001 mg/kg to 50 mg/kg of body weight.

27

28 41. The method of claim 39, wherein the therapeutically effective amount is in the range of
29 0.01 mg/kg to about 25 mg/kg of body weight.

30

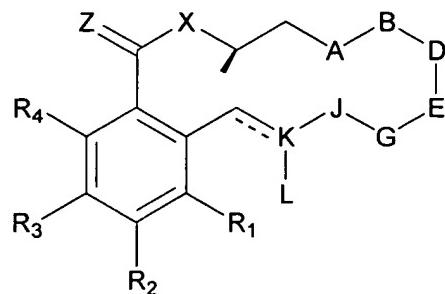
1 42. The method of claim 39, said method further comprising administering one or more
2 additional therapeutic agents in combination with the compound.

3
4 43. The method of claim 42, wherein the one or more additional therapeutic agents comprises
5 a anticancer agent

7 44. The method of claim 39, wherein the cancer comprising Rb negative cells is small cell
8 lung cancer, glioblastoma or retinoblastoma.

10 45. A method for inhibiting the growth of or killing Rb negative cancer cells, said method
11 comprising:

contacting the cells with an amount of a compound effective to inhibit the growth of or kill Rb negative cancer cells, which compound has the structure:



wherein the dotted line --- represents a bond, whereby a double bond is present, or the dotted line --- is absent, whereby a single bond is present;

18 R₁ is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
19 alkylheteroaryl moiety, or N(R_A)₂, wherein each occurrence of R_A is independently hydrogen, a
20 protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
21 moiety;

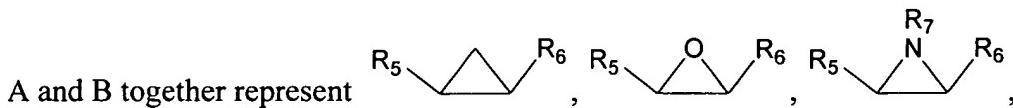
22 R₂ is hydrogen, halogen, cyano, -OR_B, -N(R_B)₂, -SR_B, -O(C=O)R_B, -N(R_B)(C=O)(R_B),
23 -C(O)R_B, -C(O)OR_B, -CON(R_B)₂, -OCO₂R_B, or an aliphatic, heteroaliphatic, aryl, heteroaryl,
24 alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_B is independently hydrogen, a
25 protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
26 moiety;

1 R₃ is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
2 alkylheteroaryl moiety, or -N(R_C)₂, wherein each occurrence of R_C is independently hydrogen, a
3 protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
4 moiety;

5 R₄ is hydrogen, halogen, cyano, -OR_D, -N(R_D)₂, -SR_D, -O(C=O)R_D, -N(R_D)(C=O)(R_D),
6 -C(O)R_D, -C(O)OR_D, -CON(R_D)₂, -OCO₂R_D, or an aliphatic, heteroaliphatic, aryl, heteroaryl,
7 alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_D is independently hydrogen, a
8 protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
9 moiety;

10 Z is O, S or NR_E, wherein R_E is hydrogen, a protecting group, an aliphatic,
11 heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or OR_F, wherein R_F is
12 hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
13 alkylheteroaryl moiety;

14 X is O, S or NR_G, wherein R_G is hydrogen or lower alkyl;



16 -CHR₅-CHR₆- , -CR₅=CR₆- , wherein R₅ and R₆ are each independently hydrogen, halogen,
17 cyano, -OR_J, -N(R_J)₂, -SR_J, -O(C=O)R_J, -O(S=O)R_J , -N(R_J)(C=O)(R_J), -C(=O)R_J, -C(=O)OR_J,
18 -CON(R_J)₂, -OCO₂R_J, -OS(=O)OR_J or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
19 alkylheteroaryl moiety, wherein each occurrence of R_J is independently hydrogen, a protecting
20 group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and
21 wherein R₇ is hydrogen, a protecting group, -OR_K, -SR_K, -C(O)OR_K, -C(O)NR_K, -S(O)₂R_K , -
22 O(C=O)R_K, -N(R_K)(C=O)(R_K), -C(O)R_K, -C(O)OR_K, -CON(R_K)₂, -OCO₂R_K, or an aliphatic,
23 heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence
24 of R_K is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl,
25 heteroaryl, alkylaryl, or alkylheteroaryl moiety, or when A and B together represent -CHR₅-
26 CHR₆- , R₅ and R₆ taken together represent a substituted or unsubstituted 3-7 membered aliphatic,
27 heteroaliphatic, aryl or heteroaryl ring,

28 D and E together represent -CHR₈-CHR₉- , -CR₈=CR₉- , wherein R₈ and R₉ are each
29 independently hydrogen or lower alkyl;

1 G and J together represent -CHR₁₀-CHR₁₁-, -CR₁₀=CR₁₁-, wherein R₁₀ and R₁₁ are each
2 independently hydrogen or lower alkyl;

3 K and L together represent C=O, C=S, CH-CH₃, CH-CH(R_L)₂, C=C(R_L)₂, -CH₂-,
4 -C(-S(CH₂)₃S)-, CH-OR_L, CH-SR_L, CH-N(R_L)₂, CH-N(R_L)(C=O)(R_L), C=N-O-R_L, CH-N=O,
5 C=C(R_L)-N(R_L)₂, C=N-R_L, C=N-N(R_L)₂, or, if the dotted line --- represents a bond, whereby a
6 double bond is present, then K and L together represent C-N(R_L)₂, wherein each occurrence of
7 R_L is independently hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl,
8 alkylaryl, or alkylheteroaryl moiety, or two occurrences of R_L taken together represent a 3 to 7-
9 membered cyclic aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety;

10 whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently
11 be substituted or unsubstituted, cyclic or acyclic, or branched or unbranched, and each aryl,
12 heteroaryl, alkylaryl, and alkylheteroaryl moiety may be substituted or unsubstituted;

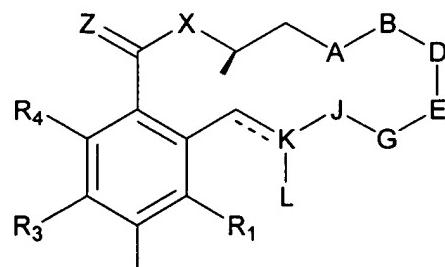
13 wherein one or any two of R₁, R_A, R₂, R_B, R₃, R_C, R₄, R_D, R₅, R₆, R_J, or R_L are optionally
14 a linker covalently bonded to a compound selected from the group consisting of radicicol,
15 monocillin, analogues of radicicol and monocillin, geldanamycin, analogues of geldanamycin,
16 and steroids; and

17 pharmaceutically acceptable derivatives thereof.

18
19 46. The method of claim 45, wheren the Rb negative cancer cells are small cell lung cancer,
20 glioblastoma or retinoblastoma cells.

21
22 47. A method for the synthesis of a compound having the structure (I):

23



1 wherein the dotted line --- represents a bond, whereby a double bond is present, or
2 the dotted line --- is absent, whereby a single bond is present;

3 R₁ is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
4 alkylheteroaryl moiety, or N(R_A)₂, wherein each occurrence of R_A is independently hydrogen, a
5 protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
6 moiety;

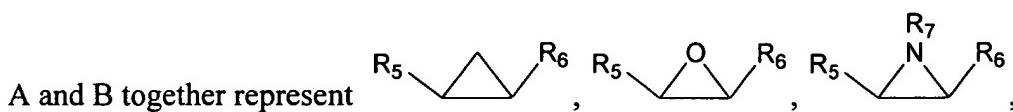
7 R₂ is hydrogen, halogen, cyano, -OR_B, -N(R_B)₂, -SR_B, -O(C=O)R_B, -N(R_B)(C=O)(R_B),
8 -C(O)R_B, -C(O)OR_B, -CON(R_B)₂, -OCO₂R_B, or an aliphatic, heteroaliphatic, aryl, heteroaryl,
9 alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_B is independently hydrogen, a
10 protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
11 moiety;

12 R₃ is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
13 alkylheteroaryl moiety, or -N(R_C)₂, wherein each occurrence of R_C is independently hydrogen, a
14 protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
15 moiety;

16 R₄ is hydrogen, halogen, cyano, -OR_D, -N(R_D)₂, -SR_D, -O(C=O)R_D, -N(R_D)(C=O)(R_D),
17 -C(O)R_D, -C(O)OR_D, -CON(R_D)₂, -OCO₂R_D, or an aliphatic, heteroaliphatic, aryl, heteroaryl,
18 alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_D is independently hydrogen, a
19 protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
20 moiety;

21 Z is O, S or NR_E, wherein R_E is hydrogen, a protecting group, an aliphatic,
22 heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or OR_F, wherein R_F is
23 hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
24 alkylheteroaryl moiety;

25 X is O, S or NR_G, wherein R_G is hydrogen or lower alkyl;



27 -CHR₅-CHR₆-, -CR₅=CR₆-, wherein R₅ and R₆ are each independently hydrogen, halogen,
28 cyano, -OR_J, -N(R_J)₂, -SR_J, -O(C=O)R_J, -O(S=O)R_J, -N(R_J)(C=O)(R_J), -C(=O)R_J, -C(=O)OR_J,
29 -CON(R_J)₂, -OCO₂R_J, -OS(=O)OR_J or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
30 alkylheteroaryl moiety, wherein each occurrence of R_J is independently hydrogen, a protecting

1 group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and
2 wherein R₇ is hydrogen, a protecting group, -OR_K, -SR_K, -C(O)OR_K, -C(O)NR_K, -S(O)₂R_K, -
3 O(C=O)R_K, -N(R_K)(C=O)(R_K), -C(O)R_K, -C(O)OR_K, -CON(R_K)₂, -OCO₂R_K, or an aliphatic,
4 heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence
5 of R_K is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl,
6 heteroaryl, alkylaryl, or alkylheteroaryl moiety, or when A and B together represent -CHR₅-
7 CHR₆-, R₅ and R₆ taken together represent a substituted or unsubstituted 3-7 membered aliphatic,
8 heteroaliphatic, aryl or heteroaryl ring,

9 D and E together represent -CHR₈-CHR₉-, -CR₈=CR₉-, wherein R₈ and R₉ are each
10 independently hydrogen or lower alkyl;

11 G and J together represent -CHR₁₀-CHR₁₁-, -CR₁₀=CR₁₁-, wherein R₁₀ and R₁₁ are each
12 independently hydrogen or lower alkyl;

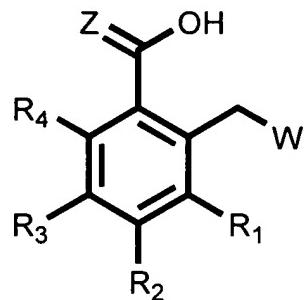
13 K and L together represent C=O, C=S, CH-CH₃, CH-CH(R_L)₂, C=C(R_L)₂, -CH₂-,
14 -C(-S(CH₂)₃S)-, CH-OR_L, CH-SR_L, CH-N(R_L)₂, CH-N(R_L)(C=O)(R_L), C=N-O-R_L, CH-N=O,
15 C=C(R_L)-N(R_L)₂, C=N-R_L, C=N-N(R_L)₂, or, if the dotted line --- represents a bond, whereby a
16 double bond is present, then K and L together represent C-N(R_L)₂, wherein each occurrence of
17 R_L is independently hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl,
18 alkylaryl, or alkylheteroaryl moiety, or two occurrences of R_L taken together represent a 3 to 7-
19 membered cyclic aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety;

20 whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently
21 be substituted or unsubstituted, cyclic or acyclic, or branched or unbranched, and each aryl,
22 heteroaryl, alkylaryl, and alkylheteroaryl moiety may be substituted or unsubstituted;
23 wherein one or any two of R₁, R_A, R₂, R_B, R₃, R_C, R₄, R_D, R₅, R₆, R_J, or R_L are optionally a linker
24 covalently bonded to a compound selected from the group consisting of radicicol, monocillin,
25 analogues of radicicol and monocillin, geldanamycin, analogues of geldanamycin, and steroids;

26 said method comprising:

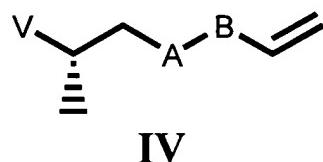
27 (1) providing a benzoic acid component having the structure:

28



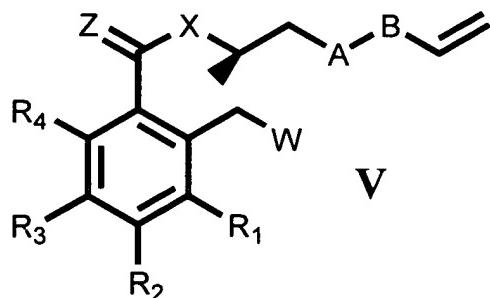
II

wherein R₁-R₄ and Z are as defined above, and wherein W is halogen; and reacting the benzoic acid component with a chiral component (**IV**) having the structure:



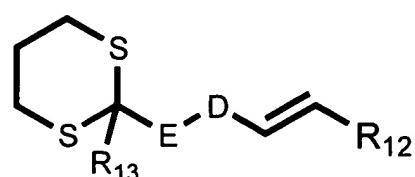
IV

wherein A and B are as defined above, and wherein V is NHR_G, wherein R_G is hydrogen or lower alkyl; SH; or OH in the presence of an esterification reagent to generate an intermediate (**V**) having the structure:



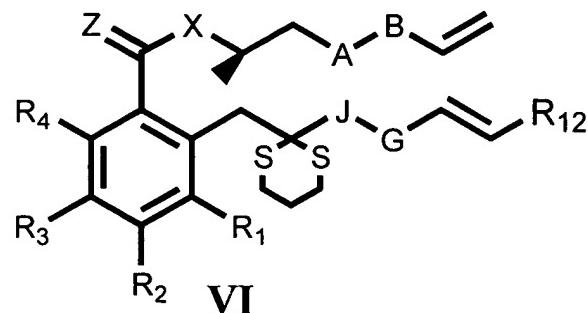
V

(2) reacting the intermediate (**V**) with a dithiane having the structure (**III**):



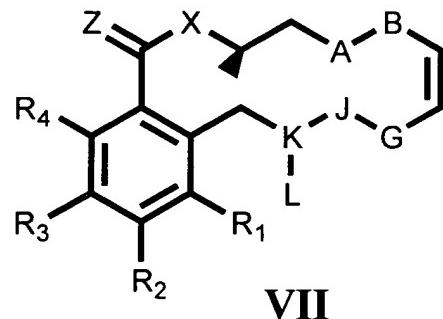
III

1
2 wherein R₁₃ is hydrogen or an alkali metal salt and wherein R₁₂ is hydrogen or lower
3 alkyl under conditions to add the dithiane to generate an intermediate (**VI**) having the structure:
4



(3) if any one or more of R₁-R₄ is an unprotected thio, amino or hydroxyl group,
optionally protecting said unprotected group;

(4) cyclizing the compound in the presence of an olefin metathesis catalyst to generate
the compound (**VII**):



(5) optionally further reacting (**VII**) with one or more reagents to diversify and
optionally deprotecting the macrolide to generate the compound (**I**).

48. The method of claim 47, wherein the step of esterification is performed using
diethylazodicarboxylate (DIAD) in the presence of triphenylphosphine or trifurylphosphine.

49. The method of claim 47, wherein the step of olefin metathesis is performed using an
olefin metathesis catalyst.

1 50. The method of claim 47, wherein the step of olefin metathesis is performed using a
2 ruthenium-based olefin metathesis catalyst.

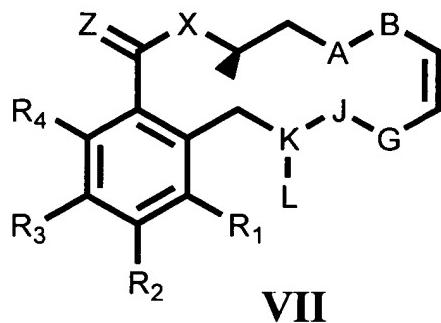
3

4 51. The method of claim 50, wherein the step of olefin metathesis is performed using Ru(1,3-
5 dimesityl-4,5-dihydro-imidazol-2-ylidene)(=CHCH=C(CH₃)₂)PCp₃Cl₂.

6

7 52. A method for synthesis of a macrocycle having the structure (VII):

8



VII

wherein the dotted line --- represents a bond, whereby a double bond is present, or the dotted line --- is absent, whereby a single bond is present;

R₁ is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or N(R_A)₂, wherein each occurrence of R_A is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R₂ is hydrogen, halogen, cyano, -OR_B, -N(R_B)₂, -SR_B, -O(C=O)R_B, -N(R_B)(C=O)(R_B), -C(O)R_B, -C(O)OR_B, -CON(R_B)₂, -OCO₂R_B, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_B is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

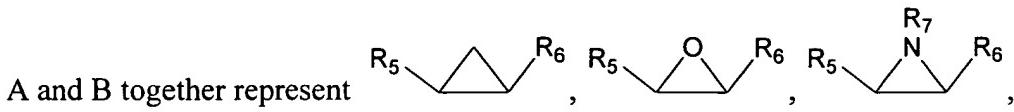
R₃ is hydrogen, halogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or -N(R_C)₂, wherein each occurrence of R_C is independently hydrogen, a protecting group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety;

R₄ is hydrogen, halogen, cyano, -OR_D, -N(R_D)₂, -SR_D, -O(C=O)R_D, -N(R_D)(C=O)(R_D),

1 -C(O)R_D, -C(O)OR_D, -CON(R_D)₂, -OCO₂R_D, or an aliphatic, heteroaliphatic, aryl, heteroaryl,
2 alkylaryl, or alkylheteroaryl moiety, wherein each occurrence of R_D is independently hydrogen, a
3 protecting group or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl
4 moiety;

5 Z is O, S or NR_E, wherein R_E is hydrogen, a protecting group, an aliphatic,
6 heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, or OR_F, wherein R_F is
7 hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
8 alkylheteroaryl moiety;

9 X is O, S or NR_G, wherein R_G is hydrogen or lower alkyl;

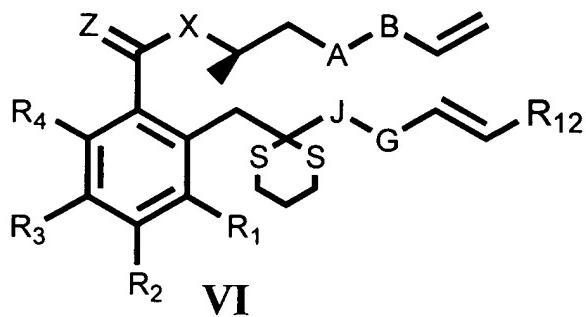


11 -CHR₅-CHR₆-, -CR₅=CR₆-, wherein R₅ and R₆ are each independently hydrogen, halogen,
12 cyano, -OR_J, -N(R_J)₂, -SR_J, -O(C=O)R_J, -O(S=O)R_J, -N(R_J)(C=O)(R_J), -C(=O)R_J, -C(=O)OR_J,
13 -CON(R_J)₂, -OCO₂R_J, -OS(=O)OR_J or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or
14 alkylheteroaryl moiety, wherein each occurrence of R_J is independently hydrogen, a protecting
15 group, or an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, and
16 wherein R₇ is hydrogen, a protecting group, -OR_K, -SR_K, -C(O)OR_K, -C(O)NR_K, -S(O)₂R_K, -
17 O(C=O)R_K, -N(R_K)(C=O)(R_K), -C(O)R_K, -C(O)OR_K, -CON(R_K)₂, -OCO₂R_K, or an aliphatic,
18 heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, wherein each occurrence
19 of R_K is independently hydrogen, a protecting group or an aliphatic, heteroaliphatic, aryl,
20 heteroaryl, alkylaryl, or alkylheteroaryl moiety, or when A and B together represent -CHR₅-
21 CHR₆-, R₅ and R₆ taken together represent a substituted or unsubstituted 3-7 membered aliphatic,
22 heteroaliphatic, aryl or heteroaryl ring,

23 G and J together represent -CHR₁₀-CHR₁₁-, -CR₁₀=CR₁₁-, wherein R₁₀ and R₁₁ are each
24 independently hydrogen or lower alkyl;

25 K and L together represent C=O, C=S, CH-CH₃, CH-CH(R_L)₂, C=C(R_L)₂, -CH₂-,
26 -C(-S(CH₂)₃S)-, CH-OR_L, CH-SR_L, CH-N(R_L)₂, CH-N(R_L)(C=O)(R_L), C=N-O-R_L, CH-N=O,
27 C=C(R_L)-N(R_L)₂, C=N-R_L, C=N-N(R_L)₂, or, if the dotted line --- represents a bond, whereby a
28 double bond is present, then K and L together represent C-N(R_L)₂, wherein each occurrence of
29 R_L is independently hydrogen, a protecting group, an aliphatic, heteroaliphatic, aryl, heteroaryl,

1 alkylaryl, or alkylheteroaryl moiety, or two occurrences of R_L taken together represent a 3 to 7-
2 membered cyclic aliphatic, heteroaliphatic, aromatic or heteroaromatic moiety;
3 whereby each of the foregoing aliphatic and heteroaliphatic moieties may independently
4 be substituted or unsubstituted, cyclic or acyclic, or branched or unbranched, and each aryl,
5 heteroaryl, alkylaryl, and alkylheteroaryl moiety may be substituted or unsubstituted;
6
7 wherein said method comprises cyclizing the intermediate (VI):
8



wherein R₁₂ is hydrogen or lower alkyl, in the presence of an olefin metathesis catalyst to generate the compound (VII).

53. The method of claim 52, wherein the method further comprises further diversifying the compound (VII) to generate a compound having the structure (I) as defined herein.

54. The method of claim 52, wherein the step of olefin metathesis is performed using an olefin metathesis catalyst.

55. The method of claim 52, wherein the step of olefin metathesis is performed using a ruthenium-based olefin metathesis catalyst.

56. The method of claim 55, wherein the step of olefin metathesis is performed using Ru(1,3-dimesityl-4,5-dihydro-imidazol-2-ylidene)(=CHCH=C(CH₃)₂)PCp₃Cl₂.